b. assaying the level of replication of the virus.

22. (Amended) The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

25. (4X amended) A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice that is repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma.

34. (Amended) The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

REMARKS

I. Claim Status. Claims 1-48 are pending. A clean copy of the claims is enclosed for the Examiner's convenience.

(i) Amended Claims. Claims 8, 13, 15, 22, 25 and 34 have been amended without prejudice or disclaimer.

Claims 8, 15 and 25 have been amended to clarify that the repopulated liver comprises hepatocytes that are infected with a compatible mammalian hepatitis virus. These amendments do not alter the scope of the claims. Accordingly, no new matter has been added by these amendments.

Claim 8 has also been amended to recite that liver degeneration is due to expression of a uPA gene present in the genome of an immunetolerant mouse. Support for the amendment is found throughout the specification, e.g., at page 11, lines 2-7. Accordingly, no new matter has been added by the amendment of claim 8.

Claims 15 and 25 have also been amended to be drawn to a chimeric mouse or mice which have "degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse [or mice]." The specification provides implicit support for degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of an immunetolerant chimeric mouse. The specification sets forth that the uPA gene is transmissible from parents to offspring, and that crossing of hemizygous uPA mice gives rise to either hemizygous or homozygous progeny (see specification at page 11, lines 17-26 and Example 1, page 17, lines 17- 26.) One of ordinary skill in the art would understand that mice that are hemizygous and homozygous for the uPA transgene have respectively one or two copies of the uPA gene at a specified chromosomal locus in the genome. The fact that the uPA gene is present in the genome of the mice is implicit in the ability of parents to transmit the uPA gene to their offspring and the observation that the transmitted uPA gene assorts among the progeny (i.e.,

crossing of hemizygous parents gives rise to both hemizygous and homozygous progeny.) Hence, the amendment of claims 15 and 25 to call respectively for a chimeric mouse or mice with degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene that is present in the genome is supported by the specification. Accordingly, the amendments to claims 15 and 25 do not add new matter to the application.

Claims 13, 22 and 34 have been amended to change the term "transgene" to "gene," which is the antecedent term provided respectively in claims 8, 15 and 25. The amendment does not change the scope of claim 13, 22 or 34. Hence, the amendments to claims 13, 22 and 34 do not add new matter to the application.

II. Advisory Action. The amendments to claims 8, 15 and 25 address the issues raised in the Advisory Action mailed on December 3, 2002, as follows.

Claim 8 has been amended to recite that liver degeneration is due to the expression of a uPA gene present in the genome of an immunetolerant mouse. Accordingly, liver degeneration is no longer attributed to the "presence" of a uPA gene in the genome.

Claims 15 and 25 have been amended respectively to read on a mouse or mice which have degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of the mouse or mice. The term"genomic" has been removed from the claims. Accordingly, the Examiner's objections to the term "genomic" are moot.

CONCLUSION

In view of the above amendments and remarks, reconsideration of this application is respectfully requested. Based on the preceding comments and amendments, the present claims are believed to be in condition for allowance and such action is earnestly solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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Docket No: 3368/1[illegible]88-[illegible]1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Charles E. ROGLER et al.

Serial No.: 09/344,189 Art Unit: 1632

Confirmation no.: 8764

Filed: June 24, 1999 Examiner: P. Paras, Jr.

For: **CHRONIC HEPATITIS VIRUS INFECTION AND CLONAL HEPATO-CELLULAR CARCINOMA IN MOUSE REPOPULATED LIVERS**

MARK-UP TO SUPPLEMENTAL AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

January 6, 2003

Sir:

The accompanying Supplemental Amendment amends the above-referenced application as follows.

IN THE CLAIMS

Claims 8, 13, 15, 22, 25 and 34 have been amended as follows.

8. (5X amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to [the presence in the genome of said mouse] expression of a urokinase-type plasminogen

activator (uPA) gene present in the genome of said immunetolerant mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes[, said xenogenic mammalian hepatocytes] that are infected with a compatible mammalian hepatitis virus.

13. (Amended) The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for [the] said urokinase-type plasminogen activator (uPA) [trans]gene and is homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

15. (4X Amended) A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a [genomic] urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes[, and said xenogenic mammalian hepatocytes being] that are infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus.

22. (Amended) The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for [the] said urokinase-type plasminogen activator (uPA) [trans]gene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

25. (4X amended) A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to expression of a [genomic] urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice that is repopulated with transplanted xenogenic mammalian hepatocytes[, said xenogenic mammalian hepatocytes being] that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma.

34. (Amended) The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for [the] said urokinase-type plasminogen activator (uPA) [trans]gene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

Pending Claims (as of January 6, 2003)

1. (4X amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus.

2. The method of claim 1, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

3. The method of claim 1, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

4. The method of claim 1, which comprises selecting the xenogenic mammalian hepatocytes from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

5. The method of claim 1, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

6. The method of claim 1, wherein the immunetolerant mouse which has a degenerated liver is created by:

a. crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2 (RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b. crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

7. The method of claim 6, wherein the xenogenic mammalian hepatocyte is from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

8. (5X amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with a compatible mammalian hepatitis virus.

9. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

10. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

11. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes is a member selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

12. The chimeric mouse model system of claim 8, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

13. (Amended) The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and is homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

14. The chimeric mouse model system of claim 13, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

15. (4X Amended) A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus.

16. The method of claim 15, wherein the mammalian virus is at least one hepatitis virus.

17. The method of claim 15, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

18. The method of claim 15, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus prior to said transplanting.

19. The method of claim 16, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus following said repopulating step.

20. The method of claim 15, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

21. The method of claim 15, wherein the compatible mammalian virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

22. The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

23. The method of claim 22, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

24. The method of claim 15, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

25. (4X amended) A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice that is repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma.

26. The method of claim 25, which comprises comparing the presence of unique viral DNA integrations in the liver of said mouse and in a control mouse which has not been administered the test compound.

27. The method of claim 25, wherein the chimeric mouse has precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue.

28. The method of claim 27, which comprises comparing the assay in the chimeric mouse with the same assay carried out in a control mouse which has not been administered the test compound.

29. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with a hepatitis virus prior to said transplantation step.

30. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting step.

31. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulating step.

32. The method of claim 25, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

33. The method of claim 25, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

34. The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

35. The method of claim 33, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

36. The method of claim 25, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

37. (Twice amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver.

38. (Twice amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and

said degenerated liver is repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

39. (Amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; and

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver.

40. The method of claim 39 wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

41. The method of claim 40 wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

42. The method of claim 1 wherein said uPA gene encodes secreted uPA.

43. The chimeric mouse model system of claim 8 wherein said uPA gene encodes secreted uPA.

44. The method of claim 15 wherein said uPA gene encodes secreted uPA.

45. The method of claim 25 wherein said uPA gene encodes secreted uPA.

46. The method of claim 37 wherein said uPA gene encodes secreted uPA.

47. The chimeric mouse model system of claim 38 wherein said uPA gene encodes secreted uPA.

48. The method of claim 39 wherein said uPA gene encodes secreted uPA.